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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,120	10/14/2005	Tatsuo Kimura	279431US0PCT	1699

22850 7590 05/15/2009

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	**PAPER NUMBER**
1612	

NOTIFICATION DATE	DELIVERY MODE
05/15/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/553,120	KIMURA ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/15/2009, 2/18/2009, 4/28/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The response filed February 18, 2009 has been received, entered and carefully considered. The response affects the instant application accordingly:

a. Claims 1-7 have been amended.

b. Claim 8-16 has been added.

2. Claims 1-16 are pending in the case.

3. Claims 1-16 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn or moot.

6. New grounds of rejection are set forth in the current office action.

Information Disclosure Statement

7. The information disclosure statement filed 2/18/2209 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. A document is missing. It has been placed in the application file, but the information referred to therein has not been considered.

8. The information disclosure statement filed 2/18/2009 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because there is no translation for Hyojun. It has been placed in the application file, but the information referred to therein

has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

New Grounds of Rejection

9. Due to the amendment of the claims the new grounds of rejection are applied.

10. Additionally, Examiner regrets the delay, but upon conference review of the specification, the unpredictability of the art, and the uncertain predictive value of the animal model in the specification, the following rejection is applied:

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The conditions of glaucoma, diabetic retinopathy, retinal artery obstruction, retinal venous obstruction, and retinopathy of prematurity which is disclosed in the specification are highly unpredictable conditions that are difficult to treat whereby the rat

ligation model presented does not show predictive value to establish a predictive correlation for use in a subject in need thereof such as a human, for the different conditions claimed, particularly as the mechanisms involved in the diseases can be different. An example is Stargardt's disease (inherited macular degeneration) which has no treatment.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the treatment of glaucoma, diabetic retinopathy, retinal artery obstruction, retinal venous obstruction, macular degeneration, and retinopathy of prematurity by administering the claimed compound (elected compound is 1-[3-(2-(1-benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol or T-817-MA).

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

In regards to the animal model, while the model is used to represent in the lab for several ischemic related disease such as glaucoma (Masuzawa et al.), the animal model does not provide adequate predictive value for treatment of the diseases claimed.

As addressed in Rosenbaum et al. (Functional and Morphologic Comparison...) there are differences between models, and while the ERG is a more sensitive parameter then conventional histopathology, the timing of the measurement is as issue of accuracy. Even the duration of ischemia has an impact on the post-ischemic recovery as after 30 minutes of ischemia with either model (the specification uses the SL model at 30 minutes), there was progressive b-wave recovery to nearly 75% of the pre-ischemic baseline 7 days later with no significant retinal structural changes.

Pang et al. (Acute effect of glaucoma medication on rat intraocular pressure) addresses the predictive value of the rat model for glaucoma. Pang addressed that the rat has been used in glaucoma research but model only has predictive value of some mechanisms but did not have predictive value of others as their responses were not identical to those observed in humans (Abstract, Discussion). The Foundation Fighting Blindness (Animal Model for Studying inherited Degenerative Retinal Disease) addresses that while there are many proposed animal models for Age-related macular degeneration, primates are the only laboratory mammal have a true macula limiting the availability of ideal animal models for this disease and that the animal model currently available mimic some but not all aspects of the pathology of AMD as the model involve

relatively young animal eyes and human AMD occur after decades. (Age-related macular degeneration section).

Zhang et al. (Activation of the Mitochondrial Apoptotic Pathway in a Rat Model of Central Retinal Artery Occlusion) addresses that animal models to simulate the features of central retinal artery occlusion such as increasing intraocular pressure or ligation of the optic nerve can garner much information but with drawbacks. The increased intraocular pressure model can induce a more global ischemic insult and the ligation model (used in the instant specification)occludes the posterior ciliary arteries occluding uveal blood supply and the central retinal artery. The mechanical damage to the neuronal cells influences the interpretation of result employing these models. As a result, the model does not accurately represent the clinical exhibition of central retinal artery occlusion in humans. It is noted that as the central retinal artery and vein run with each other, the same issues would apply to the model for central venous retinal occlusion.

The conditions themselves are unpredictable and difficult to treat. Schmidt-Erfurth (Management of neovascular age-related macular degeneration-previously submitted) addresses Age-related Macular Degeneration and how only recently gaining new insights in the pathogenesis of the disease are allowing for improved treatment for the management of the disease, but not cure as the etiology is still not clear for those skilled in the art and treatment currently is direct to slowing the progression but not recovery of lost vision. Additionally while there are new options being investigated, the efficacy is still being investigated. The Merck Manual (Age-Related Macular

Degeneration-previously submitted) supports that there is no known etiology for age-related macular degeneration. The prognosis is also unpredictable as addressed in www.wrongdiagnosis.com (about prognosis). Stargardt's disease which is an inherited form of macular degeneration in children and young adults has no treatment at all (MayoClinic.com-Stargardt's disease: Can it be treated?).

The Merck Manual (Diabetic Retinopathy-previously submitted) states that diabetic retinopathy management is with control of the diabetes and laser coagulation but treatment is designed to prevent further loss, not recovery (Prognosis and Treatment). This is also supported by the Mayo Clinic (Diabetic retinopathy-Treatments and drugs) which states that the treatment depends on the type of retinopathy, severity, and how well it may respond as surgery can slow or stop the progress of diabetic retinopathy but is not a cure as diabetes is a lifelong condition and future retinal damage and vision loss is possible. The National Eye Institute addresses that retinopathy of prematurity is unpredictable, the treatment destroys some side vision, the long term side effects are unknown, treatment decreases the chances for vision loss be does not always prevent it, not all respond to treatment, and the disease may get worse (http://www.nei.nih.gov/health/rop/-Retinopathy of Prematurity (ROP)).

(5) The relative skill of those in the art:

The relative skill is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the delivery of elected compound of 1-[3-(2-(1-benzothiophen-5-yl)ethoxy)propyl]-3-azetidinol maleate (or T-817-MA) in the single working example for an ischemic ligation rat model to the optic nerve. As addressed above, the diseases claimed are unpredictable and difficult to treat and the model utilized does not have predictive value for treatment of the conditions claimed for a subject in need thereof with these conditions, particularly humans. In addition that there is not current treatment for Stargardt's disease, an inherited form of macular degeneration.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the high unpredictability in the art as evidenced therein, and the lack of predictive value of the rat model for treatment of the claimed conditions in a subject such as a human, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Response to Arguments

13. Due to the translation provided, Applicant receives the foreign priority date.

14. In regards to Applicant's argument to the copy of Xuan et al. for AMD treatment is not persuasive as Xuan suggests that AMD is a choroidal vascular abnormality/insufficiency and was published in 1999, and Schmidt-Erfurth et al. addresses that there are many other mechanisms involved not yet discovered and is a current review as it is dated 2007. Additionally, as addressed by the enablement

rejection above, there is no current treatment for Stargardt's disease, an inherent form of macular degeneration.

Conclusion

15. Claims 1-16 are rejected.

16. Applicant's amendment necessitated the new ground of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612